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FILE 'CAPLUS' ENTERED AT 08:41:48 ON 23 JUL 2004
              E GONZALEZ HECTOR/IN,AU
L1            34 S E1-12
L2         26174 S CYCLODEXTRIN
L3            15 S L1 AND 2
L4       1738813 S POLYMER?
L5             5 S L3 AND L4
L6             1 S 2002:487421/AN
L7        225801 S BIOLOGICAL TRANSPORT
L8            22 S L2 AND L4 AND L7
L9            21 S L8 NOT L5
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L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:487421 CAPLUS
DOCUMENT NUMBER: 137:47645
TITLE: Preparation of adamantyl-polyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents
INVENTOR(S): Hwang, Pun Suzie; **Gonzalez, Hector**; Davis, Mark E.; Bellocq, Nathalie; Cheng, Jianjun
PATENT ASSIGNEE(S): California Institute of Technology, USA; Insert Therapeutics, Inc.
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002049676 | A2 | 20020627 | WO 2001-US48620 | 20011219 |
| WO 2002049676 | A3 | 20021227 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002029065 | A5 | 20020701 | AU 2002-29065 | 20011219 |
| US 2003008818 | A1 | 20030109 | US 2001-21312 | 20011219 |
| US 2003017972 | A1 | 20030123 | US 2001-21294 | 20011219 |
| EP 1351710 | A2 | 20031015 | EP 2001-990201 | 20011219 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2001016346 | A | 20040706 | BR 2001-16346 | 20011219 |

PRIORITY APPLN. INFO.:
US 2000-256341P P 20001219
US 2000-256344P P 20001219
US 2001-293543P P 20010529
WO 2001-US48620 W 20011219

AB The invention provides a composition containing particulate composite of a **polymer** with a formula of adamantyl-(CH2)n-Ja-PEGx-Lb-(functional group)y wherein J is NH, C(O)NH(CH2)d, NHC(O)(CH2)d, XH2SS, CO2,(CH2)eOP(O)[O(CH2)e-adamantyl]O, peptide, polypeptide, NH(CO)CHR1NH(CO)CHR1NH; R1 is (CH2)aCO2H, (CH2)aCONH2; PEG is O(CH2CH2O)z; where z is 2-500; L is H, NH2, NH(CO)(CH2)e(CO)CH2, SO2CH:CH2, SS, CO2, carbohydrate residue; a is 0-1, b is 0-1; d is 0-6; e is 1-6; yr is 0-1, x is 0-1, and a therapeutic agent. The composition also contains a complexing agent. The **polymer** interacts with the complexing agent in a host-guest or a guest-host interaction to form an inclusion complex. A therapeutic composition of the invention may be used to deliver the therapeutic agent and to treat various disorders. Both the **polymer** of the particulate composite and the complexing agent may be used to introduce functionality into the therapeutic composition The invention also relates to a method of preparing a composition The method combines a therapeutic agent, a **polymer** having host or guest functionality, and a complexing agent having guest or host functionality to form the therapeutic composition The complexing agent forms an inclusion complex with the **polymer**. The invention also relates to a method of delivering a therapeutic agent. According to the method, a therapeutically effective amount of a therapeutic composition of the invention is administered to a mammal (e.g. human or animal) in recognized need of the therapeutic.

L6 1 ANSWERS CAPLUS COPYRIGHT 2004 ACS on STN
IC ICM A61K047-48
CC 35-8 (Chemistry of Synthetic High Polymers)
Section cross-reference(s): 6, 33, 34, 63
TI Preparation of adamantyl-polyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents
ST transferrin human adamantylpolyethylene glycol inclusion cyclodextrin therapeutic prepn; cell uptake adamantylpolyethylene glycol inclusion cyclodextrin therapeutic prepn; adamantylpolyethylene glycol sugar peptide inclusion therapeutic prepn human
IT Transferrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human; preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT DNA
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(human; preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT Drugs
Human
Inclusion reaction
(preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT Carbohydrates, preparation
Glycols, preparation
Peptides, preparation
Polymers, preparation
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT Inclusion compounds
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT Biological transport
(uptake; preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT 9014-00-0, Luciferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT 57-88-5DP, Cholesterol, inclusion complexes 91-20-3DP, Naphthalene, inclusion complexes 281-23-2DP, Adamantane, inclusion complexes 2292-79-7DP, inclusion complexes 26282-59-7DP, cyclodextrin thioethers 81644-55-5DP, polyethoxylated ether derivs. 107658-43-5DP, adamantane-modified 254912-05-5P 254912-07-7P 254912-09-9P 264257-54-7DP, reaction products with polymeric cyclodextrin thioamidoamides 275354-52-4P 275354-53-5DP, lactosylamine adducts 275354-54-6P 438490-85-8P 438490-87-0DP, adducts with lactose 438490-89-2DP, fluorescein derivs. 438490-89-2P 438490-90-5P 438490-95-0DP, human transferrin bound
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT 63-42-3D, succinimidyl derivs. 118-31-0, 1-Naphthalenemethanamine 768-94-5, 1-Aminoadamantane 870-46-2, tert-Butyl carbazate 1676-73-9 3406-84-6 3416-24-8, Glucosamine 4942-47-6, Tricyclo[3.3.1.13,7]decane-1-acetic acid 7535-00-4 7585-39-9, β-Cyclodextrin 14620-72-5 14641-93-1, α-Lactose 14651-42-4 17176-77-1, Dibenzyl phosphite 17768-41-1, Tricyclo[3.3.1.13,7]decane-1-methanamine 27072-45-3 32130-27-1 38285-78-8 39927-08-7 51974-68-6, Sodium 2-aminoethylthiolate 57757-57-0 58537-94-3 62087-82-5 67413-34-7 68528-80-3 123502-57-8 152310-58-2 155919-13-4 174569-25-6 254912-03-3 264257-54-7 275354-51-3 438490-88-1 438490-91-6 438490-94-9 438490-97-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)
IT 29390-66-7P 35625-91-3P 67217-55-4P 73499-21-5P 76700-72-6P 81644-55-5P 98126-99-9P 101652-40-8P 107658-43-5P 159790-69-9P

162825-08-3P 254912-04-4P 275354-53-5P 275354-55-7P 438490-86-9P
438490-87-0P 438490-92-7P 438490-93-8P 438490-95-0P 438490-96-1P
438490-98-3P 438490-99-4P 438491-00-0P 438491-01-1P 438491-02-2P
438491-03-3P 438491-04-4P 438491-05-5P 438491-06-6P 438491-07-7P
438491-08-8P 438491-09-9P 438491-10-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of adamantylpolyethylene glycol containing sugar and peptide residues and inclusion complexes as therapeutic agents)

L9 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:341917 CAPLUS
DOCUMENT NUMBER: 140:385470
TITLE: Contribution of Cholesterol and Phospholipids to Inhibitory Effect of Dimethyl-β-**Cyclodextrin** on Efflux Function of P-glycoprotein and Multidrug Resistance-Associated Protein 2 in Vinblastine-Resistant Caco-2 Cell Monolayers
AUTHOR(S): Arima, Hidetoshi; Yunomae, Kiyokazu; Morikawa, Tadatoshi; Hirayama, Fumitoshi; Uekama, Kaneto
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, 862-0973, Japan
SOURCE: Pharmaceutical Research (2004), 21(4), 625-634
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose. The purpose of this study is to reveal the contribution of membrane components to the inhibitory effect of 2,6-di-O-methyl-β-**cyclodextrin** (DM-β-CyD) on P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2) function in vinblastine-resistant Caco-2 (Caco-2R) cell monolayers. Methods. The transport of rhodamine-123 and 2',7'-bis(2-carboxy- ethyl)-5(6)-carboxyfluorescein (BCECF) was studied in Caco-2R cell monolayers. P-gp and MRP2 residing in the monolayers and releasing in cell supernatants were detected by Westerrn blotting. The mRNA levels of MDR1 and MRP2 were detected by reverse transcription-**polymerase** chain reaction (RT-PCR) method. Cholesterol, phospholipids, and proteins were mainly determined by each assay kit. Results. Of various β- **cyclodextrin** derivs. (β-CyDs), DM-β-CyD most significantly impaired the efflux function of P-gp and MRP2 without changing cell viability and membrane integrity. The treatment with CyDs did not change the mRNA levels of MDR1 and MRP2. DM-β-CyD lowered cholesterol content and P-gp level in caveolar membranes. In addition, DM-β-CyD released not only cholesterol and phospholipids but also proteins including P-gp and MRP2 from apical membranes of the monolayers. Conclusions. DM-β-CyD may impair P-gp and MRP2 function in Caco-2R cell monolayers, probably, at least in part, through the release of these transporters from the apical membranes of monolayers, and the exertion of the inhibitory effect of DM-β-CyD may require the extraction of not only cholesterol but also phospholipids from the monolayers.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:974595 CAPLUS
DOCUMENT NUMBER: 141:28277
TITLE: Absorption enhancers in pulmonary protein delivery
AUTHOR(S): Hussain, Alamdar; Arnold, John J.; Khan, Mansoor A.; Ahsan, Fakhrul
CORPORATE SOURCE: School of Pharmacy, Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center, Amarillo, TX, 79106, USA
SOURCE: Journal of Controlled Release (2004), 94(1), 15-24
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Extensive research efforts have been directed towards the systemic administration of therapeutic proteins and poorly absorbed macromols. via various nontraditional, injection-free administration sites such as the lung. As a portal for noninvasive delivery, pulmonary administration possesses several attractive features including a large surface area for drug absorption. Nevertheless, achieving substantial bioavailability of proteins and macromols. by this route has remained a challenge, chiefly due to poor absorption across the epithelium. The lungs are relatively impermeable to most drugs when formulated without an absorption enhancer/promoter. In an attempt to circumvent this problem, many novel absorption promoters have been tested for enhancing the systemic availability of drugs from the lungs. Various protease inhibitors, surfactants, lipids, **polymers** and agents from other classes have been tested for their efficacy in improving the systemic availability of protein and macromol. drugs after pulmonary administration. The purpose of this article is to provide the reader with a summary of recent advances made in the field of pulmonary protein delivery utilizing absorption enhancers. This report reviews the various

agents used to increase the bioavailability of these drugs from the lungs, their mechanisms of action and effectiveness, and their potential for toxicity.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:833021 CAPLUS
DOCUMENT NUMBER: 140:91327
TITLE: Cholesterol Depletion Impairs Vascular Reactivity to Endothelin-1 by Reducing Store-Operated Ca2+ Entry Dependent on TRPC1
AUTHOR(S): Bergdahl, Andreas; Gomez, Maria F.; Dreja, Karl; Xu, Shang-Zhong; Adner, Mikael; Beech, David J.; Broman, Jonas; Hellstrand, Per; Swaerd, Karl
CORPORATE SOURCE: Department of Physiological Sciences, Lund University, S-21 84, Swed.
SOURCE: Circulation Research (2003), 93(9), 839-847
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The reactivity of the vascular wall to endothelin-1 (ET-1) is influenced by cholesterol, which is of possible importance for the progression of atherosclerosis. To elucidate signaling steps affected, the cholesterol acceptor methyl-β- **cyclodextrin** (mβcd, 10 mmol/L) was used to manipulate membrane cholesterol and disrupt caveolae in intact rat arteries. In endothelium-denuded caudal artery, contractile responsiveness to 10 nmol/L ET-1 (mediated by the ETA receptor) was reduced by mβcd and increased by cholesterol. Neither ligand binding nor colocalization of ETA and caveolin-1 was affected by mβcd. Ca2+ inflow via store-operated channels after depletion of intracellular Ca2+ stores was reduced in mβcd-treated caudal arteries, as shown by Mn2+ quench rate and intracellular [Ca2+] response. Expression of TRPC1, 3, and 6 was detected by reverse transcriptase-**polymerase** chain reaction, and colocalization of TRPC1 with caveolin-1 was reduced by mβcd, as seen by immunofluorescence. Part of the contractile response to ET-1 was inhibited by Ni2+ (0.5 mmol/L) and by a TRPC1 blocking antibody. In the basilar artery, exhibiting less store-operated channel activity than the caudal artery, ET-1-induced contractions were insensitive to the TRPC1 blocking antibody and to mβcd. Increased store-operated channel activity in basilar arteries after organ culture correlated with increased sensitivity of ET-1 contraction to mβcd. These results suggest that cholesterol influences vascular reactivity to ET-1 by affecting the caveolar localization of TRPC1.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:613973 CAPLUS
DOCUMENT NUMBER: 139:243641
TITLE: Initiation and transduction of stretch-induced RhoA and Rac1 activation through caveolae: Cytoskeletal regulation of ERK translocation
AUTHOR(S): Kawamura, Shuji; Miyamoto, Shigeki; Brown, Joan Heller
CORPORATE SOURCE: Department of Pharmacology, University of California, San Diego, La Jolla, CA, 92093, USA
SOURCE: Journal of Biological Chemistry (2003), 278(33), 31111-31117
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Rho family small GTPases play a crucial role in mediating cellular responses to stretch. However, it remains unclear how force is transduced to Rho signaling pathways. We investigated the effect of stretch on the activation and caveolar localization of RhoA and Rac1 in neonatal rat cardiomyocytes. In unstretched cardiomyocytes, RhoA and Rac1 were detected in both caveolar and non-caveolar fractions as assessed using detergent-free floatation anal. Stretching myocytes for 4 min activated RhoA and Rac1. By 15 min of stretch, RhoA and Rac1 had dissociated from caveolae, and there was decreased copptn. of RhoA and Rac1 with caveolin-3. To determine whether compartmentation of RhoA and Rac1 within caveolae was necessary for stretch signaling, we disrupted caveolae with Me β- **cyclodextrin** (MβCD). Treatment with 5 mM MβCD for 1 h dissociated both RhoA and Rac1 from caveolae. Under this condition, stretch failed to activate RhoA or Rac1. Stretch-induced actin

cytoskeletal organization was concomitantly impaired. Interestingly the ability of stretch to activate extracellular signal-regulated kinase (ERK) was unaffected by MβCD treatment, but ERK translocation to the nucleus was impaired. Stretch-induced hypertrophy was also inhibited. Actin cytoskeletal disruption with cytochalasin-D also prevented stretch from increasing nuclear ERK, whereas actin **polymn**. with jasplakinolide restored nuclear translocation of activated ERK in the presence of MβCD. We suggest that activation of RhoA or Rac1, localized in a caveolar compartment, is essential for sensing externally applied force and transducing this signal to the actin cytoskeleton and ERK translocation.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:402957 CAPLUS
DOCUMENT NUMBER: 139:146969
TITLE: Differential mobilization of newly synthesized cholesterol and biosynthetic sterol precursors from cells
AUTHOR(S): Lusa, Sari; Heino, Sanna; Ikonen, Elina
CORPORATE SOURCE: Department of Molecular Medicine, National Public Health Institute, Helsinki, Finland
SOURCE: Journal of Biological Chemistry (2003), 278(22), 19844-19851
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous work demonstrates that the biosynthetic precursor of cholesterol, desmosterol, is released from cells and that its efflux to high d. lipoprotein or phosphatidylcholine vesicles is greater than that of newly synthesized cholesterol (Johnson, W. J., Fischer, R. T., Phillips, M. C., and Rothblat, G. H. (1995) J. Biol. Chemical 270, 25037-25046). Here we report that the release of individual precursor sterols varies with the efflux of newly synthesized zymosterol being greater than that of lathosterol and both exceeding that of newly synthesized cholesterol when using either methyl-β- **cyclodextrin** or complete serum as acceptors. The transfer of newly synthesized lathosterol to methyl-β- **cyclodextrin** was inhibited by actin **polymn** . but not by Golgi disassembly whereas that of newly synthesized cholesterol was inhibited by both conditions. Newly synthesized lathosterol associated with cellular detergent-resistant membranes more rapidly than newly synthesized cholesterol. Upon efflux to serum, newly synthesized cholesterol precursors associated with both high and low d. lipoproteins. Stimulation of the formation of direct endoplasmic reticulum-plasma membrane contacts was accompanied by enhanced efflux of newly synthesized lathosterol but not of newly synthesized cholesterol to serum acceptors. The data indicate that the efflux of cholesterol precursors differs not only from that of cholesterol but also from each other, with the more polar zymosterol being more avidly effluxed. Moreover, the results suggest that the intracellular routing of cholesterol precursors differs from that of newly synthesized cholesterol and implicates a potential role for the actin cytoskeleton and endoplasmic reticulum-plasma membrane contacts in the efflux of lathosterol.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:121526 CAPLUS
DOCUMENT NUMBER: 139:296732
TITLE: Mechanistic studies of the effect of hydroxypropyl-β- **cyclodextrin** on in vitro transdermal permeation of corticosterone through hairless mouse skin
AUTHOR(S): Shaker, D. S.; Ghanem, A.-H.; Li, S. K.; Warner, K. S.; Hashem, F. M.; Higuchi, W. I.
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: International Journal of Pharmaceutics (2003), 253(1-2), 1-11
CODEN: IJPHDE; ISSN: 0378-5173
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Literature reports reveal that the issue of whether **cyclodextrins**

may act as skin permeation enhancers has not been resolved. Accordingly, in vitro skin transport studies were conducted to address this question. Corticosterone (3H-CS and/or non-radiolabeled CS) was chosen as the model permeant for transport expts. with hairless mouse skin (HMS) and with a synthetic cellulose membrane of 500 mol. weight cut off (MWCO), the latter to help establish baseline behavior. Hydroxypropyl-β-**cyclodextrin** (HPβCD) was selected as the representative **cyclodextrin**. The CS/HPβCD complexation constant was determined both from solubility data (saturation conditions) in phosphate buffered saline (PBS), pH 7.4 and with data obtained from PBS/silicone **polymer** partitioning expts., the latter expts. permitting the determination of the complexation constant at low CS concns. These results were used in the calcns. of the free CS concns. in the donor chamber of the transport expts. The CS transport expts. were conducted at CS solubility saturation and under supersatn. (resulting from autoclaving at 121°) conditions as well at very low (tracer level) concns. The effect of polyvinylpyrrolidone as a solution additive was also evaluated. The following were the key outcomes of this study. Contrary to literature reports, there was no evidence that HPβCD is an enhancer for CS transport through HMS. The CS permeability coefficient values obtained with HMS in all of the expts. were found to be the same within exptl. error when calculated on the basis of the free CS concentration as the driving force for permeation. The constancy of the permeability coefficient in the presence and absence of HPβCD is interpreted to mean that, in these expts., HPβCD did not alter the barrier properties of HMS stratum corneum to any significant extent nor did it enhance CS transport in any other manner such as by a carrier mechanism involving the aqueous boundary layer or by a carrier mechanism within the stratum corneum.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:960660 CAPLUS
DOCUMENT NUMBER: 138:19488
TITLE: Method and pharmaceutical compositions using anti-microtubule agents for treating multiple sclerosis and other inflammatory diseases
INVENTOR(S): Hunter, William L.
PATENT ASSIGNEE(S): Angiotech Pharmaceuticals, Inc., Can.
SOURCE: U.S., 180 pp., Cont.-in-part of U.S. Appl. 2002 37,919.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6495579 | B1 | 20021217 | US 1998-88546 | 19980601 |
| US 2002037919 | A1 | 20020328 | US 1997-980549 | 19971201 |
| US 6515016 | B2 | 20030204 | | |
| EP 1070502 | A2 | 20010124 | EP 2000-123557 | 19971202 |
| EP 1070502 | A3 | 20011017 | | |
| EP 1070502 | B1 | 20030604 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| EP 1090637 | A2 | 20010411 | EP 2000-123537 | 19971202 |
| EP 1090637 | A3 | 20010912 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| EP 1092433 | A2 | 20010418 | EP 2000-123534 | 19971202 |
| EP 1092433 | A3 | 20010912 | | |
| EP 1092433 | B1 | 20030806 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002226399 | A2 | 20020814 | JP 2001-401899 | 19971202 |
| WO 9962510 | A2 | 19991209 | WO 1999-CA464 | 19990601 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002013298 | A1 | 20020131 | US 1999-368463 | 19990804 |

| | | | | |
|---|---|---|---|---|
| US 2002183380 | A1 | 20021205 | US 2002-67467 | 20020205 |
| US 6689803 | B2 | 20040210 | | |
| US 2003157187 | A1 | 20030821 | US 2002-172737 | 20020613 |

PRIORITY APPLN. INFO.:
US 1996-32215P P 19961202
US 1997-63087P P 19971024
US 1997-980549 A2 19971201
EP 1997-945697 A3 19971202
JP 1998-524997 A3 19971202
US 1998-88546 A 19980601
US 1999-368463 B1 19990804
US 1999-368871 A1 19990804

AB Methods and compns. for treating or preventing inflammatory diseases, e.g. psoriasis or multiple sclerosis, are provided, comprising delivering to the site of inflammation an anti-microtubule agent (e.g. paclitaxel), or analog or derivative thereof.

REFERENCE COUNT: 171 THERE ARE 171 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:736897 CAPLUS
DOCUMENT NUMBER: 137:242166
TITLE: Delivery systems and methods for noscapine and noscapine derivatives useful as anticancer agents
INVENTOR(S): Joshi, Harish C.; Ye, Keqiang; Kapp, Judith; Landen, Jaren; Archer, David; Armstrong, Cheryl; Liu, Fuqiang
PATENT ASSIGNEE(S): Emory University, USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of U.S. 6,376,516.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002137762 | A1 | 20020926 | US 2002-56913 | 20020125 |
| US 6673814 | B2 | 20040106 | | |
| US 6376516 | B1 | 20020423 | US 2000-582375 | 20000926 |

PRIORITY APPLN. INFO.:
US 1997-57037P P 19970819
US 2000-582375 A2 20000926
US 2001-264357P P 20010126
WO 1998-US14979 W 19980720

OTHER SOURCE(S): MARPAT 137:242166
AB The invention provides methods useful for the treatment of neoplastic diseases, tumor cells, and the treatment of cancer delivering noscapine compds. The invention also provides various methods of delivering such compds., combinations of treatments, and altering such compds. to enhance their effectiveness. Synthesis of noscapine compds. is described.

L9 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:429408 CAPLUS
DOCUMENT NUMBER: 137:11002
TITLE: Administering pharmaceuticals to the mammalian central nervous system
INVENTOR(S): Lerner, Eduard N.
PATENT ASSIGNEE(S): Neth.
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U. S. Ser. No. 77,123.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002068080 | A1 | 20020606 | US 1998-197133 | 19981120 |
| US 6410046 | B2 | 20020625 | | |
| US 2002082583 | A1 | 20020627 | US 2002-50183 | 20020118 |
| US 2004064127 | A1 | 20040401 | US 2003-687816 | 20031020 |

PRIORITY APPLN. INFO.:
WO 1996-EP5086 A1 19961119
US 1998-77123 A2 19980520
US 1998-197133 A2 19981120
US 2002-50183 A3 20020118

AB A device, methods and pharmaceutical compns. are disclosed for transnasal or transocular drug delivery to the central nervous system using a

combination of electrotransport or phonophoresis with chemical permeation enhancers. The permeation enhancers may be polycationic **polymers**, chelators, acylcarnitines, Ca modulators, **cyclodextrins**, or bile salts. A solvent such as DMSO may be used.

L9 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:724737 CAPLUS
DOCUMENT NUMBER: 136:374676
TITLE: Preparation and characterization of insulin-loaded acrylic hydrogels containing absorption enhancers
AUTHOR(S): Uchida, Takahiro; Toida, Yuka; Sakakibara, Sadako; Miyanaga, Yohko; Tanaka, Hiromi; Nishikata, Mayumi; Tazuya, Keiko; Yasuda, Noriko; Matsuyama, Kenji
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Nishinomiya, 663-8179, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (2001), 49(10), 1261-1266
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objectives of this study were to prepare insulin-loaded acrylic hydrogel formulations containing various absorption enhancers, to perform in vitro and in vivo characterization of these formulations, and to evaluate the factors which affecting insulin availability on rectal delivery of insulin using this hydrogel system. The acrylic block copolymer of methacrylic acid and methacrylate, Eudispert, was used to make the hydrogel formulations. As absorption enhancers, 2,6-di-O-methyl-β-**cyclodextrin** (DM-β-CyD), lauric acid (C12), or the sodium salt of C12 (C12Na), were incorporated into the hydrogels. In an in vitro release test, the release rate of insulin from the hydrogels decreased as the **polymer** concentration of the hydrogel increased. The addition of C12Na to the hydrogel further increased the insulin release rate, which was greater at higher concns. of the enhancer. A portion of the C12Na was found to remain bound to the acrylic **polymer** in dissoln. medium. Serum insulin levels were determined at various time points after the administration of insulin solution or insulin-loaded (50 units/kg body weight) Eudispert hydrogels containing 5% (weight/weight) of C12, C12Na, or DM-β-CyD to in situ loops in various regions of the rat intestine. The most effective enhancement of insulin release was observed with formulations containing C12Na. The bioavailability of insulin from the hydrogels was lower than that from the insulin solns. Hydrogel formulations containing 7% or 10% Eudispert remained in the rectum for 5 h after rectal administration. However, the 5% (weight/weight) C12Na solution stained with Evan's-blue had diffused out and the dye had reached the upper intestinal tract within 2 h. Finally, the rectal administration of insulin-loaded hydrogels, containing 4%, 7%, or 10% (weight/weight) Eudispert and 5% (weight/weight) of enhancer (C12, C12Na, or DM-β-CyD) to normal rats was shown to decrease serum glucose concns. The greatest effect was found with insulin-loaded 7% (Eudispert) hydrogel containing C12Na which having considerable large insulin release rate and bioadhesive characteristics.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:567803 CAPLUS
DOCUMENT NUMBER: 133:250173
TITLE: Characterization of apolipoprotein-mediated HDL generation induced by cAMP in a murine macrophage cell line
AUTHOR(S): Abe-Dohmae, Sumiko; Suzuki, Shogo; Wada, Youichiro; Aburatani, Hiroyuki; Vance, Dennis E.; Yokoyama, Shinji
CORPORATE SOURCE: Biochemistry I, Medical School, Nagoya City University, Nagoya, 467-8601, Japan
SOURCE: Biochemistry (2000), 39(36), 11092-11099
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Murine macrophage RAW264 were investigated for their response to lipid-free apolipoproteins. Preincubation of the cells with 300 μM dibutyryl cyclic (dBc) AMP for 16 h induced specific binding of apolipoprotein (apo) A-I to the cells and apoA-I-mediated HDL formation with cellular lipids, neither of which was detected in the absence of dBcAMP. Dose-dependent changes of the apoA-I specific binding and the apoA-I-mediated cholesterol release were largely superimposable. ApoA-II also mediated lipid release after the treatment of the cells with dBcAMP

and effectively displaced the apoA-I binding to the cells. In contrast, cellular cholesterol efflux to lipid microemulsion and to 2-(hydroxypropyl)-β- **cyclodextrin** was uninfluenced by the dBcAMP treatment. To induce the cellular reactivity with apoA-I, the incubation with dBcAMP required at least 6 h. Actinomycin D, cycloheximide, puromycin, and brefeldin A suppressed both the induction of apoA-I-mediated lipid release and the apoA-I specific binding to the cells. Anal. of the expression level of ABC1 mRNA by using reverse transcription-**polymerase** chain reaction and oligonucleotide arrays revealed that ABC1 mRNA was already expressed in the dBcAMP-untreated cells, and the dBcAMP treatment for 16 h enhanced its expression 9-13-fold. The authors conclude that dBcAMP selectively induces apolipoprotein-mediated cellular lipid release and accordingly high-d. lipoprotein generation by inducing specific binding of apolipoprotein, but does not influence diffusion-mediated lipid efflux. The cell-apolipoprotein interaction seems to depend on cellular protein biosynthesis and transport. A substantial increase in the level of ABC1 mRNA caused by the dBcAMP treatment indicates that ATP-binding cassette transporter 1, the protein product of ABC1, may directly be responsible for the interaction, but the question about the absence of the interaction with its baseline expression level remains.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:213347 CAPLUS
DOCUMENT NUMBER: 132:345727
TITLE: Phosphatidylinositol 4,5-bisphosphate induces actin-based movement of raft-enriched vesicles through WASP-Arp2/3
AUTHOR(S): Rozelle, A. L.; Machesky, L. M.; Yamamoto, M.; Driessens, M. H. E.; Insall, R. H.; Roth, M. G.; Luby-Phelps, K.; Marriott, G.; Hall, A.; Yin, H. L.
CORPORATE SOURCE: Departments of Physiology and Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
SOURCE: Current Biology (2000), 10(6), 311-320
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Phosphatidylinositol 4,5-bisphosphate (PIP2) has been implicated in the regulation of the actin cytoskeleton and vesicle trafficking. It stimulates de novo actin **polymn**. by activating the pathway involving the Wiskott-Aldrich syndrome protein (WASP) and the actin-related protein complex Arp2/3. Other studies show that actin **polymerizes** from cholesterol-sphingolipid-rich membrane microdomains called "rafts", in a manner dependent on tyrosine phosphorylation. Although actin has been implicated in vesicle trafficking, and rafts are sites of active phosphoinositide and tyrosine kinase signaling that mediate apically directed vesicle trafficking, it is not known whether phosphoinositide regulation of actin dynamics occurs in rafts, or if it is linked to vesicle movements. Results: Overexpression of type I phosphatidylinositol phosphate 5-kinase (PIP5KI), which synthesizes PIP2, promoted actin **polymn**. from membrane-bound vesicles to form motile actin comets. Pervanadate (PV), a tyrosine phosphatase inhibitor, induced comets even in the absence of PIP5KI overexpression. PV increased PIP2 levels, suggesting that it induces comets by changing PIP2 homeostasis and by increasing tyrosine phosphorylation. Platelet-derived growth factor (PDGF) enhanced PV-induced comet formation, and these stimuli together potentiated the PIP5KI effect. The vesicles at the heads of comets were enriched in PIP5KIs and tyrosine phosphoproteins. WASP-Arp2/3 involvement was established using dominant-neg. WASP constructs. Endocytic and exocytic markers identified vesicles enriched in lipid rafts as preferential sites of comet generation. Extraction of cholesterol with methyl-β-**cyclodextrin** reduced comets, establishing that rafts promote comet formation. Conclusions: Sphingolipid-cholesterol rafts are preferred platforms for membrane-linked actin **polymn**. This is mediated by in situ PIP2 synthesis and tyrosine kinase signaling through the WASP-Arp2/3 pathway. Actin comets may provide a novel mechanism for raft-dependent vesicle transport and apical membrane trafficking.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:622928 CAPLUS
DOCUMENT NUMBER: 131:355947

TITLE: Drug-**cyclodextrin** complexation in the presence of water-soluble **polymers**: enhanced solubility and percutaneous transport
AUTHOR(S): Masson, Mar; Loftsson, Thorsteinn
CORPORATE SOURCE: Department of Pharmacy, University of Iceland, Reykjavik, 105, Iceland
SOURCE: ACS Symposium Series (1999), 737(Polysaccharide Applications), 24-45
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 60 refs. For variety of reasons, including production capabilities, toxicol. and cost, the amount of **cyclodextrin** that can be used in drug and cosmetic formulations will be limited. In order to use less **cyclodextrin** the complexation efficacy (Kc[So] or [D·CD]/[CD]) must be increased. We have shown that the complexation efficacy of various lipophilic drugs can be significantly increased by heating **cyclodextrin** drug solution up to 120-130°C for 20-40 min in the presence of small amount of water soluble **polymers**. At least 30% enhancement in complexation efficacy is common and in some cases over 200% increase is observed Phase-solubility studies revealed that this was due to an apparent increase in the complexation stability constant (Kc). The percutaneous transport through hairless mouse skin in-vitro from drug-**cyclodextrin** solns. was increased up to 200% by addition **polymer** and in-vivo studies showed that the bioavailability of for example dexamethasone from eye-drop solns. could be increased about four fold. Formulation of drugs with **cyclodextrins** and **polymers** can thus enhance the attractive properties of **cyclodextrins** as pharmaceutical excipients.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:750406 CAPLUS
DOCUMENT NUMBER: 130:100557
TITLE: Co-administration of a water-soluble **polymer** increases the usefulness of **cyclodextrins** in solid oral dosage forms
AUTHOR(S): Savolainen, Jouko; Jarvinen, Kristiina; Taipale, Hannu; Jarho, Pekka; Loftsson, Thorsteinn; Jarvinen, Tomi
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, FIN-70211, Finland
SOURCE: Pharmaceutical Research (1998), 15(11), 1696-1701
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of **cyclodextrins** (β-CD, HP-β-CD and (SBE)7m-β-CD), and co-administration of a water-soluble **polymer** (HPMC) and **cyclodextrins**, on the oral bioavailability of glibenclamide in dogs was investigated. Effects of **cyclodextrins** on the aqueous solubility of glibenclamide, with and without hydroxypropylmethyl cellulose (HPMC), were determined by a phase-solubility method. Solid inclusion complexes were prepared by freeze-drying. Glibenclamide was administered orally and i.v. to beagle dogs. Aqueous solubility of glibenclamide increased as a function of **cyclodextrin** concentration, showing an AL-type diagram for β-CD and an Ap-type diagrams for both of the β-CD derivs. studied. HPMC enhanced the solubilizing effect of **cyclodextrins** , but did not affect the type of phase-solubility diagram. Orally administered glibenclamide and its phys. mixture with HP-β-CD showed poor absolute bioavailability, while orally administered glibenclamide/ **cyclodextrin**-complexes significantly enhanced the absolute bioavailability of glibenclamide. Orally administered glibenclamide/β-CD/HPMC and glibenclamide/(SBE)7m-β-CD/HPMC complexes showed similar absolute bioavailability compared to formulations not containing HPMC, even though 80% (in the case of (SBE)7m-β-CD) or 40% (in the case of β-CD) less **cyclodextrin** was used. The oral bioavailability of glibenclamide was significantly increased by **cyclodextrin** complexation. HPMC increased the solubilizing effect of **cyclodextrins** and, therefore, the amount of **cyclodextrin** needed in the solid dosage form was significantly reduced by their co-administration. In conclusion, the pharmaceutical usefulness of **cyclodextrins** in oral administration may be substantially improved by co-administration of a water-soluble **polymer**.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:133393 CAPLUS
DOCUMENT NUMBER: 128:286262
TITLE: Solubilization of quercetin, and permeability study of quercetin and rutin to rabbit duodenal mucosa
AUTHOR(S): Chun, In Koo; Seo, Eun Ha
CORPORATE SOURCE: College of Pharmacy, Dongduk Women's University, Seoul, 136-714, S. Korea
SOURCE: Yakhak Hoechi (1998), 42(1), 59-69
CODEN: YAHOA3; ISSN: 0513-4234
PUBLISHER: Pharmaceutical Society of Korea
DOCUMENT TYPE: Journal
LANGUAGE: Korean
AB To increase the solubility of quercetin, which is a practically insol. flavonoid of Ginkgo biloba leaf, the effects of nonaq. vehicles, their cosolvents, water-soluble **polymers** and modified **cyclodextrins** were observed Polyethylene glycols, diethyleneglycol monoethyl ether, and their cosolvents with water showed a good solvency toward quercetin. Also the aqueous solns. of povidone, copolyvidone and Cremophor RH 40 were effective in solubilizing quercetin. Complex formation of quercetin with β- **cyclodextrin** (β-CD), dimethyl-β- **cyclodextrin** (DMCD), 2-hydroxypropyl-β- **cyclodextrin** (HPCD) and β- **cyclodextrin** sulfobutyl ether (SBCD) in water was investigated by solubility method at 37°. The addition of CDs in water markedly increased the solubility of quercetin with increasing the concentration Solubilization efficiency by CDs was in the order of SBCD»DMCD>HPCD>β-CD. The dissoln. rates of quercetin from solid dispersions with copolyvidone, povidone and HPCD were much faster than those of drug alone and corresponding phys. mixts., and exceeded the equilibrium solubility (3.03±1.72 μg/mL). The permeation of quercetin through duodenal mucosa did not occur even in the presence of enhancers such as bile salts, but the permeation was observed when the mucus layer was scraped off. This was due to the fact that quercetin had a strong binding to mucin (58.5 μg/mg mucin). However rutin was permeable to the duodenal mucosa. The addition of enhancer significantly increased the permeation of rutin in the order of Na glycocholate ≤ Na deoxycholate < ammonium glycyrrhizinate.

L9 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:116571 CAPLUS
DOCUMENT NUMBER: 128:172042
TITLE: **Cyclodextrins** as co-enhancers in dermal and transdermal drug delivery
AUTHOR(S): Loftsson, Thorsteinn; Masson, M.; Sigurdsson, H. H.; Magnusson, P.; Le Goffic, F.
CORPORATE SOURCE: Department Pharmacy, University Iceland, Reykjavik, IS-127, Iceland
SOURCE: Pharmazie (1998), 53(2), 137-139
CODEN: PHARAT; ISSN: 0031-7144
PUBLISHER: Govi-Verlag Pharmazeutischer Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of **cyclodextrins** and **polymers** on the skin permeability of testosterone was investigated. Solubilization of testosterone by 2-hydroxypropyl-β- **cyclodextrins** DS: 2.92 (HPβCD) resulted in a notable increase in transdermal delivery of the drug from an aqueous solution through hairless mouse skin. Addition of an excess **cyclodextrin** resulted in a decreased dermal or transdermal drug delivery. Hydroxypropyl methylcellulose, polyvinylpyrrolidone, and CM-cellulose enhanced the testosterone permeability by 150, 100, and 100%, resp. Pretreatment of the skin with glycerol monoether extract caused a 20- to 35-fold increase in the permeability coeffs. In an oil-in-water emulsion, 60 and 40% increase in the flux was observed when 5% HPβCD and 0.5% glycerol monoether extract, resp. were added to the emulsion. About 80% increase in the flux were achieved when both HPβCD and the extract were added.

L9 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:194523 CAPLUS
DOCUMENT NUMBER: 126:242770
TITLE: **Cyclodextrins** as skin penetration enhancers. Effects of **polymers** on **cyclodextrin** complexation and transdermal drug delivery
AUTHOR(S): Loftsson, Thorsteinn; Sigurdardottir, Anna M.
CORPORATE SOURCE: Department of Pharmacy, University of Iceland,

Reykjavik, IS-127, Iceland
SOURCE: Proceedings of the International Symposium on Cyclodextrins, 8th, Budapest, Mar. 31-Apr. 2, 1996 (1996), 403-406. Editor(s): Szejtli, J.; Szente, L. Kluwer: Dordrecht, Neth.
CODEN: 64CDAL
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The flux of hydrocortisone and enalaprilat was determined from aqueous vehicles containing various amts. of 2-hydroxypropylβCD, carboxymethylβCD, randomly methylated βCD or maltosylβCD through hairless mouse skin. When the drug was in suspension, the flux was increased as the **cyclodextrin** (CD) concentration was increased. The flux decreased at higher CD concns., when all the drug was in solution Maximum flux through the skin was obtained when just enough CD was used to keep all the drug in solution Addition of small amount of a water-soluble **polymer**, such as hydroxypropyl Me cellulose or polyvinylpyrrolidone, to the aqueous complexation medium, and heating in sealed container to 120-140°C for 20-40 min, resulted in up to 200% larger drug permeability compared to prepns. containing no **polymer**.

L9 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:194484 CAPLUS
DOCUMENT NUMBER: 126:242761
TITLE: Conjugates based on **cyclodextrins** and poly(ethylene oxide) as complexation and transport agents
AUTHOR(S): Topchieva, I. N.; Elezkaya, S. V.; Polyakov, V. A.; Karezin, K. I.
CORPORATE SOURCE: Department of Chemistry, Moscow State University, Moscow, 119899 MGU, Russia
SOURCE: Proceedings of the International Symposium on Cyclodextrins, 8th, Budapest, Mar. 31-Apr. 2, 1996 (1996), 125-128. Editor(s): Szejtli, J.; Szente, L. Kluwer: Dordrecht, Neth.
CODEN: 64CDAL
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A new series of branched derivs. of CDs is described. They result from the **polymn**. of ethylene oxide initiated with secondary hydroxyl groups of CDs. These conjugates are water soluble, amorphous liqs. Complexation properties of these compds. with 4-nitrophenol and calcium acetylhomotaurinate (CAHT) are studied. It was shown that CAHT as a drug combined with conjugates shows a prominent anticonvulsive effect in the expts. in vivo. This effect is due to the complex crosses the brain endothelium barrier with the following release of drug.

L9 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:117230 CAPLUS
DOCUMENT NUMBER: 126:229499
TITLE: Interaction of supramolecular assembly with hairless rat stratum corneum
AUTHOR(S): Kamimura, Wataru; Ooya, Tooru; Yui, Nobuhiko
CORPORATE SOURCE: Sch. Mater. Sci., Japan Ad. Inst. Sci. Technol., Ishikawa, 923-12, Japan
SOURCE: Journal of Controlled Release (1997), 44(2,3), 295-299
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polyrotaxanes are well known as a supramol. assembly in which many cyclic compds. are threaded onto a linear **polymeric** chain capped with bulky end-groups. In this paper, a polyrotaxane consisting of α-CDs and PEG capped with biodegradable peptide moieties was synthesized, and the interaction with stratum corneum of hairless rat skin was examined by means of a differential scanning calorimetry. The hydroxypropylated polyrotaxane was found to interact with lipid components in the stratum corneum: bound water content was significantly decreased although ordered lipid bilayers were maintained. Thus, it is suggested that our designed polyrotaxane can be feasible as novel candidates for transdermal penetration enhancers.

L9 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:522119 CAPLUS
DOCUMENT NUMBER: 125:177303
TITLE: Effects of **cyclodextrins** and **polymers** on topical drug delivery to the eye - evaluations in humans

AUTHOR(S): Loftsson, T.; Stefansson, E.; Frioriksdottir, H.; Kristinsson, J.K.
CORPORATE SOURCE: Department of Pharmacy, University of Iceland, Reykjavik, IS-127, Iceland
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1996), 23rd, 453-454
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Addition of HPMC to aqueous hydroxypropyl β- **cyclodextrins** eye drop solns. and heating the solns. in an autoclave both enhanced the **cyclodextrin** complexation of drugs, resulting in enhanced drug solubilization, and the drug permeability into the eye.

L9 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:208789 CAPLUS
DOCUMENT NUMBER: 116:208789
TITLE: Construction of an Escherichia coli export-affinity vector for expression and purification of foreign proteins by fusion to cyclomaltodextrin glucanotransferase
AUTHOR(S): Hellman, Jukka; Mantsala, Pekka
CORPORATE SOURCE: Dep. Biochem., Univ. Turku, Turku, SF-20500, Finland
SOURCE: Journal of Biotechnology (1992), 23(1), 19-34
CODEN: JBITD4; ISSN: 0168-1656
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A novel export-affinity fusion vector employing the gene encoding cyclomaltodextrin glucanotransferase (CGTase; cgt) from Bacillus circulans var. alkalophilus (ATCC 21783) is described. CGTase binds to various sugar **polymers**, which makes it simple to purify it to near homogeneity in a single step. The CGTase fusion protein vector was constructed by deleting the translational stop codons from the gene encoding CGTase (cgt) by in vitro mutagenesis. As models, genes encoding Escherichia coli alkaline phosphatase (APase; phoA) and Bacillus stearothermophilus (ATCC 12980) α-amylase (BStA; amy) were fused to cgt. Overexpression of wild-type CGTase and the hybrid proteins under the control of the lac promoter caused a leaky phenotype in E. coli, the outer membrane became permeable, which enabled the adsorption of the fusion proteins directly from the culture medium onto α-**cyclodextrin** (α-CD)-coupled agarose. The hybrid proteins were eluted from the column with α-CD solution under mild conditions at pH 7.5. The CGTase-APase fusion had a good in vivo stability, whereas the CGTase-BStA' was less stable. In the latter case, according to protein sequencing, the proteolytically sensitive site was on the BStA' side of the fusion. The C-terminus of CGTase was stable against proteolysis as shown by narrow pH range isoelec. focusing. The fused enzymes retained their biol. activities.